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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/080,127	05/15/98	BLINKOVSKY A	5253.200-US

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HM22/0518

EXAMINER	
TURNER,S	
ART UNIT	**PAPER NUMBER**
1647	19

DATE MAILED: 05/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/080,127	Blinkovsky
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 3-15-01

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 130-169 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 130-169 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. The Art Unit of U.S. Patent application SN 09/080,127 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1647.

2. The amendments filed 11-27-00 and 3-15-01, declaration and statement filed 11-27-00 have been entered into the record and have been fully considered. Claims 90-129 are canceled. Claims 130-169 are pending.

3. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner in view of the new rejections set forth below.

New Rejections

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 130-133, 136-145, 151-155, 158-168 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO's: 1 and 2 which correspond respectively to the nucleotide sequence and the amino acid sequence of an *Aspergillus* aminopeptidase. These SEQ ID NO's meet the written description provisions of 35 USC 112, first paragraph. However, the claims are directed to or encompass corresponding polypeptides from other species, mutated peptides, peptides produced from allelic variants, splice variants, peptide sequences that have a recited degree of identity and peptides which are encoded by hybridizing nucleic acids. None of these sequences meets the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO's:1 and 2 of the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to

lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO's:1 and 2 , but not the full breadth of claims meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicants argue that the information of the specification combined with the knowledge in the art provide sufficient guidance to one skilled in the art to isolate amino peptidases from other strains of Aspergillus. Applicants submit that the physicochemical properties of the claim are sufficient written description to inform the skilled artisan that applicants were in possession of the claimed aminopeptidases at the time the application was filed.

Applicants arguments filed 11-27-00 have been fully considered but are not persuasive. The claims encompass amino acid sequences which are not described by applicants specification, and for which there is no evidence that the encompassed alternative sequences share the physicochemical characteristics of the claims. No alternative amino acid sequences are disclosed with the exception of SEQ ID NO:2. The single species is not descriptive of a genus or family of peptides. The skilled artisan thus, would not readily recognize that applicants were in possession of the claimed invention.

6. Claims 130-133, 136-145, 151-155, 158-168 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the aminopeptidase of residues 16-

496 of SEQ ID NO:2, does not reasonably provide enablement for polypeptides of claims 130-133, 136-145, 151-155, 158-168. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation.

As to claims 130-133, 136-145, 151-155, 158-168 with respect to % identity, allelic variants and fragments which retain aminopeptidase activity, Choh et al., PNAS 77(6):3211-3214, June 1980, clearly teach that even highly related polypeptides with different amino acid sequences exhibit distinct biological activities and divergent immunoreactivity. The specification does not teach any peptide which corresponds to the recited % identity or fragment thereof, which retains aminopeptidase activity or possesses the physicochemical properties of; a pH optimum in the range of from about pH 7.27 to about pH 10.95 determined at ambient temperature in the presence of Ala-para-nitroanilide, a temperature stability of 90% or more relative to initial activity at pH 7.5 determined after incubation for 20 minutes at 60°C in the absence of substrate and an ability to hydrolyze a substrate containing Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Phe, Pro, Ser, Thr, Trp, Tyr, or Val at its N-terminus wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time ~~fro~~ from the N-terminus of a peptide, polypeptide or protein.

The skilled artisan recognizes the unpredictability in the art of determining functional characteristics of a peptide based on alternative structure, even for highly homologous sequences, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000, in particular abstract and Box 2.

As to claims 130-133, 136-145, 151-155, 158-168 with respect to hybridizing nucleotides, the skilled artisan recognizes that hybridizing nucleic acids are dependent upon the specific residues, the G+C content, the hybridization conditions and the length of the hybridizing sequences, see in particular Jenkins et al., PCR Methods and Applications S77-82, 1994. The specification fails to teach any hybridizing nucleic acids which encode a peptide having the recited identity, a fragment thereof, a peptide which retains aminopeptidase activity or the physicochemical properties of; a pH optimum in the range of from about pH 7.27 to about pH 10.95 determined at ambient temperature in the presence of Ala-para-nitroanilide, a temperature stability of 90% or more relative to initial activity at pH 7.5 determined after incubation for 20 minutes at 60°C in the absence of substrate and an ability to hydrolyze a substrate containing Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Phe, Pro, Ser, Thr, Trp, Tyr, or Val at its N-terminus wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time fro the N-terminus of a peptide, polypeptide or protein.

As to claims 130-133, 136-145, 151-155, 158-168 with respect to hybridization and complementary strands, the skilled artisan is well aware that the complementary nucleotides and sequences which hybridize to the coding strand, i.e., the non-coding strand, are unrelated to the

coding sequence. Thus, applicant is not enabled for the use of a vector and host cell expressing the complementary strand or hybridizing sequences which encodes a aminopeptidase because the protein encoded by the opposite strand is unrelated both structurally and functionally to aminopeptidase sequences.

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation for the skilled artisan to make and use the claimed invention.

Applicants argue that the specification provides instructions on how to obtain the polypeptides, in particular p. 4, line 9 to p. 6, line 17, that hybridization conditions and protocols are provided on p. 5, line 18 to p. 6, line 18, and that one of skill in the art would know how to identify and isolate such analogs given the teachings disclosed in the specification. Applicants argue that the claims do not recite that the complementary or hybridizing strand encodes an aminopeptidase and that one skilled in the art would understand that a sequence encoding a protein must be denatured to undergo hybridization. Applicants argue that the inventions enablement is sufficient with respect to In re Wands and that limiting the claims to the deposited strain would be contrary to In re Goffe.

Applicant's arguments filed 11-27-00 have been fully considered but they are not persuasive. The specifications guidance does not enable a skilled artisan to obtain the appropriate peptides. For example, the specification does not provide a specific probe, hybridization

conditions or a library from which an aminopeptidase with the claimed characteristics may be isolated. The artisan, based on the limited guidance is not reasonably assured of reproducibly and reliably obtaining the claimed aminopeptidases as directed. Further, the artisan would be forced, after obtaining a candidate agent to perform undue experimentation to determine the full open reading frame, express the protein and determine the peptides biological properties as well as its functional characteristics. The specification is required to be fully enabled at the time of the invention and the standard of an enabling disclosure is not one of 'make and test,' but one of make and use. The skilled artisan is well aware of the unpredictability in the art of determining functional characteristics of a peptide based on alternative (% identity and hybridizing) structure, even for highly homologous sequences, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000, in particular abstract and Box 2. Applicants do not provide evidence of reduction to practice for any other aminopeptidase other that of SEQ ID NO:2. The specification merely invites the artisan to discover other related sequences. The single species does not support the genus claim. It is noted that the skill of the art was high in In re Goffe, contrary to the instant case. For these reasons, applicants arguments are not persuasive.

7. Claims 146 and 169 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of plasmid pEJG18 in *E. coli* NRRL B-21677. Because it is not clear that cell lines possessing the properties of plasmid pEJG18 in *E. coli* NRRL B-21677 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of plasmid pEJG18 in *E. coli* NRRL B-21677, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the cell line claimed in claims 146 and 169, is required. Without publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to plasmid pEJG18 in *E. coli* NRRL B-21677 is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR § 1.801-1.809 have been met.

Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the plasmid pEJG18 in *E. coli* NRRL B-21677 cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR § 1.801-1.809 for further information concerning deposit practice.

Applicants argue that the statement under 37 CFR 1.808 under the Budapest treaty and over the attorneys signature is sufficient to complete the deposit requirements.

Applicants arguments filed 11-27-00 have been fully considered but are not persuasive as compliance with the deposit requirements requires amendment to the specification to recite the date of deposit and complete name and full street address of the depository.

8. Claims 143, 162 and 163 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 143, 162 and 163 are rejected as the claims recite medium stringency conditions, however the specification clearly defines medium stringency as hybridization under 35% formamide. The recitation of 50% formamide as medium stringency is considered new matter. The claim should be amended to either recite high stringency conditions, or alternatively 35% formamide which is consistent with the specification. See p. 5, lines 26-31.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 130-133, 136-145, 151-155, 158-168 are rejected under 35 U.S.C. 102(b) as being anticipated by Nishizawa et al., J. Biol. Chem., 269:13651-55, 1994.

Nishizawa teach a *S. cerevisiae* aminopeptidase which hybridizes with SEQ ID NO:1 as the Nishizawa sequence encodes residues 255-264 of SEQ ID NO:2. This 30 mer has a Tm=87 degrees C based on the formula Tm= 4(G+C) + 2(A+T). Therefore the sequence hybridizes under medium and high stringency conditions of 42 degrees C. Thus, the sequence anticipates the claimed invention, see in particular residues 1180-1209 of the Nishizawa nucleic acid sequence.

11. Claims 130-169 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakadai et al., Agr. Biol. Chem., 37(4):767-774, 1973.

Instant SEQ ID NO:2 is disclosed in the specification at p. 45, line 32 as exhibiting MW 58 kD on SDS PAGE. Nakadai teach a MW 61 kD polypeptide which shares the characteristics of applicants aminopeptidase, i.e., it is stable at 60 degrees, see in particular figure 9, has a pH optimum within applicants range, see in particular figures 6-8 and hydrolyzes oligopeptides at the amino terminus with particular affinity to leucine, but also cleaves other N-terminus amino acids, see in particular figure 1, 10 and Table 2. The molecular weight of the peptide is considered to be so close as to be equivalent to 58 kD. The peptide originates from Asp. oryzae. Nakadai thus appears to correlate to applicants peptide and inherently shares the amino acid sequence, absent convincing factual evidence to the contrary.

12. Claims 130-169 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakadai et al., Agr. Biol. Chem., 37(4):775-782, 1973.

Instant SEQ ID NO:2 is disclosed in the specification at p. 45, line 32 as exhibiting MW 58 kD on SDS PAGE. Nakadai teach a MW 56 kD polypeptide which shares the characteristics of applicants aminopeptidase, i.e., it is stable at 60 degrees, see in particular figures 8-9, has a pH optimum within applicants range, see in particular figures 6-7 and hydrolyzes oligopeptides at the amino terminus with particular affinity to leucine, but also cleaves other N-terminus amino acids, see in particular figure Table 2. The molecular weight of the peptide is considered to be so close as to be equivalent to 58 kD. The peptide originates from Asp. oryzae. Nakadai thus appears to correlate to applicants peptide and inherently shares the amino acid sequence, absent convincing factual evidence to the contrary.

Status of Claims

13. No claims are allowed.

Conclusion

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
May 16, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud